IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Philippe LEFEVRE et al.
Serial No.: US 10/579 919
Filed: Aug. 18, 2004
Assigned to: ROQUETTE FRERES
Examiner:

FOR: FILM-FORMING STARCHY COMPOSITION

DECLARATION UNDER RULE 132

To the Honorable Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Philippe LEFEVRE, of 3600 rue de Merville, 59660 Haverskerque – France, do solemnly declare:

THAT I have been working with the firm ROQUETTE FRERES since 28/01/1985 and that I now hold the position of Engineer as Scientific Coordinator of the Pharmaceutical Applications;

THAT I am a named inventor on the present patent application n°10/579 919, and that I am fully familiar therewith;

THAT the experiments described in example 1 of the present application were carried out under my supervision;

THAT the formulations of the Table 3 are graded by comparison between the various formulation tested with "+++" for the best performance and "0" for the worst performance, a graduation "+++" meaning an excellent result;

THAT the quotation system used for attributing the different graduations, i.e. "0", "+", "++", and "+++", takes into account the criteria that are detailed in Table 1 (see Annex 1);

THAT for number of the evaluated criteria, there is no method for determining exact values; these criteria are thus evaluated qualitatively and comparatively;

THAT the photos of figures 1 to 4 (Annex 2) to which Annex 1 refers, show the physical aspect of tablets that were evaluated according to the quotation system of Annex 1;

THAT Figures 1 and 2 of Annex 2 show tablets having a quotation "+++" for all of the evaluated criteria;

THAT Figures 3 and 4 of Annex 2 show tablets having a quotation "0" for all of the evaluated criteria and thus illustrate some undesirable coating failures:

- The white specks are the consequence of a sticking of the tablet to another tablet. During the separation of the two tablets, a piece of the film remains stuck to the other tablet and is pulled out of the coating of the first tablet. So the white colour of the non coated tablet is visible. Note that this white

surface may be after coated but the coating thickness will remain too thick.

- The colour is non homogeneous. White and pale blue corresponds to a too low deposit of coating substances. Dark blue correspond to a too high deposit. There is an important variation of the deposit of the coating solution and consequently of the thickness of the film at the surface of the tablets. This gives the orange skin aspect.

THAT essentially the same results as those obtained in Example 1 of the present application when using pea starch (35/39 % amylose) were obtained when using pea starch having an amylose content of 30 to 40 % dry/dry, in particular 31.2 ± 1 % dry/dry, 33.7 ± 1 % dry/dry, 35.6 ± 1 % dry/dry, and 38.9 ± 1 % dry/dry (determined according to Annex 3);

I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001, of Title 18, of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 2011/10/05

Philippe LEFEVRE

Example 1 – Quotation system

	0	+	++	+++
Viscosity at 25°C and 10% solid content (mPa.s)	>500	300 to 499	200 to 299	0 to 199
Strength of the film: (aspect of the tablets after an European Pharmacopeia friability test for tablets)	- All tablets have their edge damaged (removal of pieces of the film with the white color of the tablets visible)	- Some tablets have their edge damaged (removal of pieces of the film with the white color of the tablets visible)	- No visible change of the tablets but presence of colored film dust in the drum used for the test	All tablets are intact No colored dust in the drum
Smooth appearance	- Non homogeneous color from the beginning to the end - Important orange skin aspect	- Homogeneous color appearing only in the from the beginning to the end - Important orange skin aspect	- Non homogeneous color only at the beginning (less than a half of the coating time) - Low orange skin aspect	- Homogeneous color from beginning to the end of the coating - No orange skin aspect detectable without a magnifying glass
Non sticky feel	- All tablets sticking together and to the fingers - No flow at all	- Low sticking to the fingers - Flow of tablets only after shocks or vibration - Beginning of sticking of tablets together after 1 week storage	- Very low sticking to the fingers - Free flowing of the tablets - Beginning of sticking of tablets together after month storage	- No tablets sticking to the fingers - Free flowing of the tablets - No sticking of tablets together during storage
Absence of agglomeration during coating	- Presence of tablets stuck together - More than 5 % of tablets having traces of sticking	- No tablets stuck together - From 1% to 5 % of tablets having traces of sticking	-No tablets stuck together Less than 1% of tablets having traces of sticking	- No tablets stuck together - No traces of sticking
Coating appearance	- Non homogeneous color with white specks (color of the tablets visible) - Important orange skin aspect	- About homogeneous color - Important orange skin aspect	-Homogeneous color -Low orange skin aspect No traces of sticking	- Homogeneous color - No orange skin aspect detectable without a magnifying glass - No traces of sticking

European Pharmacopeia friability test for tablets : European Pharmacopeia vol. 6.0; Index 2.9.7. Friability of uncoated tablets.

Figures 1 to 4 show coated convex tablets of 13 mm diameter.

Figures 1 & 2 illustrate the required coating. These coated tablets have a quotation "+++" for all the criteria. The coating has a homogeneous blue colour.

Figures 3 & 4 illustrate some undesirable coating failure. These tablets have a quotation "0" for all the criteria

- The white specks are the consequence of a sticking of the tablet to another tablet. During the separation of the two tablets, a piece of the film remains stuck to the other tablet and is pulled out of the coating of the first tablet. So the white colour of the non coated tablet is visible. Note that this white surface may be after coated but the coating thickness will remain too thick.
- The colour is non homogeneous. White and pale blue corresponds to a too low deposit of coating substances. Dark blue correspond to a too high deposit. There is an important variation of the deposit of the coating solution and consequently of the thickness of the film at the surface of the tablets. This gives the orange skin aspect.

ANNEX 2

Figure 1

Figure 2

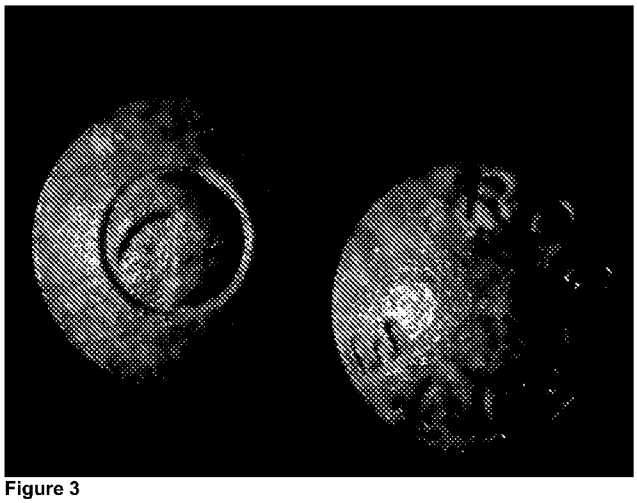

Figure 3

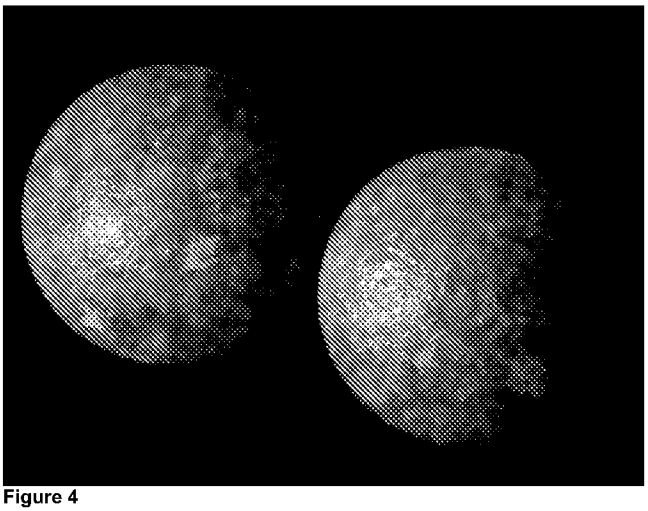

Figure 4

ANNEX 2

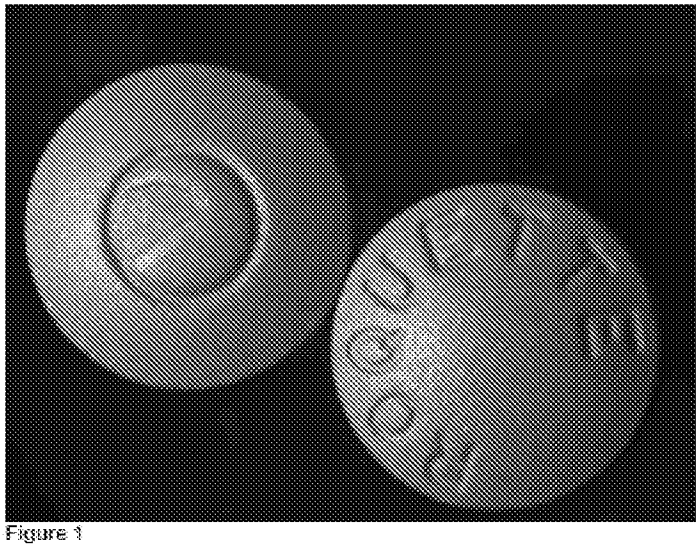

Figure 1

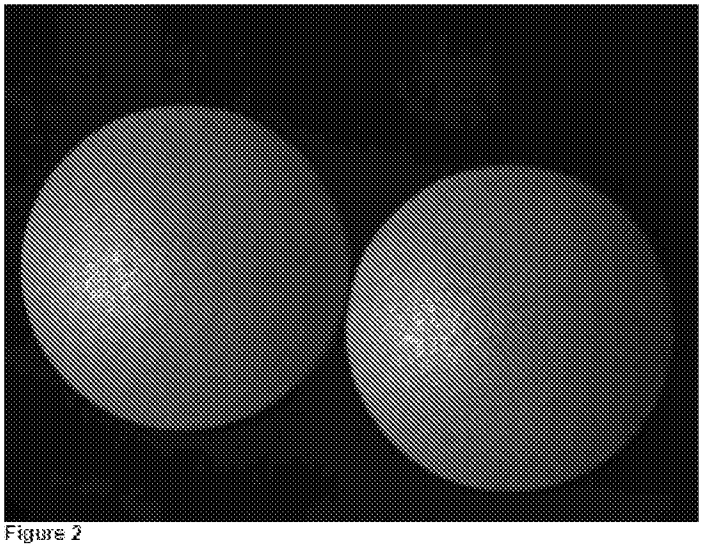

Figure 2

GRAYSCALE

ANNEX 2

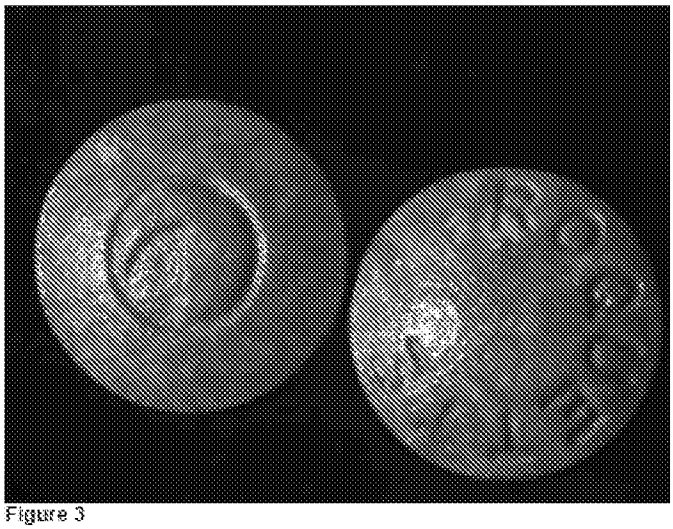

Figure 3

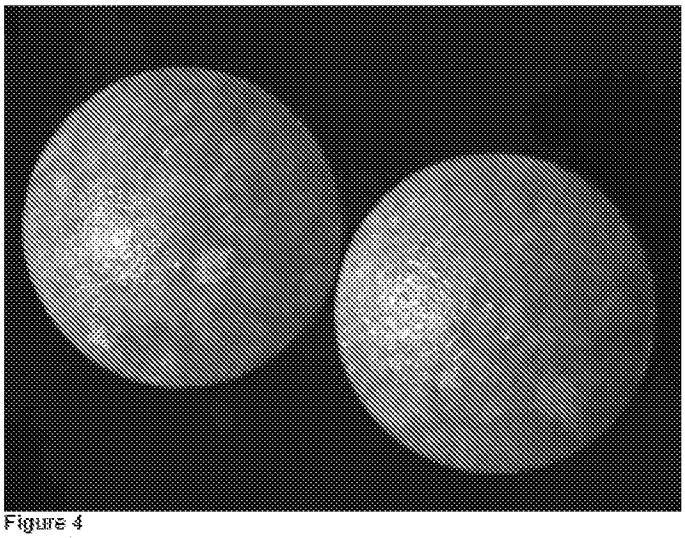

Figure 4

GRAYSCALE

ANNEX 3

ROQUETTE

ORIGIN : ROQUETTE SECTOR : DAC	**DETERMINATION OF AMYLOSE BY POTENTIOMETRIC ANALYSIS**	**MCL 045B** ISSUE no 05

ADDRESSEES

ROQUETTE

ORIGIN : ROQUETTE SECTOR : DAC	DETERMINATION OF AMYLOSE BY POTENTIOMETRIC ANALYSIS	MCL 045B ISSUE no 05

	NAME(S)	FUNCTION(S)	SIGNATURE(S)	
WRITTEN BY	D. LANOY			
TRANSLATED BY	M.O. DEVILLERS			
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	Ph. LIENART			

1 - SCOPE AND FIELD OF APPLICATION

Method for the determination of amylose in native starches.

2 - REFERENCE

MCL 002B : Loss on drying – Starches

3 - PRINCIPLE

Determination by potentiometric analysis of iodine absorbed by AMYLOSE to form a complex.

4 - REAGENTS

Use only reagents and distilled water of recognized analytical grade.

4 - 1 Distilled water or water of equivalent purity

4 - 2 Potassium iodide and potassium chloride solution

Potassium iodide e.g. Riedel de Haen Ref. 03124		166.02 g
Potassium chloride e.g. Riedel de Haen Ref. 31248		74.55 g
Distilled water (4-1)	to make	2000 ml

This solution is 0.5 N in KI and 0.5 N in KCl.

4 - 3 Iodine standard solution

1 N iodine e.g. Merck Ref. 1.09088		17,3	ml
Potassium iodide and potassium chloride solution (4-2)	to make	1000	ml

Titrate this solution with a 0.01 N sodium thiosulphate solution freshly prepared by dilution of a 0,1 N sodium thiosulphate solution (e.g. Merck Ref. 109147). T is the titre obtained in mg/ml iodine.

Keep this solution in a brown glass flask and titrate again regularly.

4 - 4 Dilute iodine solution

Exactly pipette 50 ml of the iodine standard solution (4-3) into a 250-ml volumetric flask. Dilute to volume with distilled water (4-1). Homogenise. This solution shall be daily prepared and kept in a brown glass flask.

4 - 5 0.5 N potassium iodide solution

Potassium iodide e.g. Riedel de Haen Ref. 03124		83.01	g
Distilled water (4-1)	to make	1000	ml

4 - 6 1 N potassium hydroxide solution

e.g. Merck Ref. 109108

4 - 7 0.5 N hydrochloric acid solution

e.g. Merck Ref. 109058

4 - 8 Methanol at 85° GL

Pure methanol e.g. Merck Ref. 106009		800	ml
Distilled water (4-1)	to make	1000	ml

Check the alcoholometric titre with an alcoholmeter and adjust if need be.

5 - APPARATUS

Usual laboratory apparatus and in particular :

5 - 1 METTLER DL25-type potentiometer, for instance

equipped with a platinum electrode and a reference calomel electrode or a METTLER DM140-type combined electrode, for instance.

5 - 2 Thermostatted water bath at 2 ± 0.5°C

e.g. Ministrat Hüber-type equipped with a thermometer graduated at 0.5°C at least, checked according to the instructions for use specified in the relevant manual.

5 - 3 Double-walled titration beaker

connected to the thermostatted water bath (5-2)

5 - 4 Oven allowing drying at 50-60°C

e.g. infrared oven

5 - 5 Balance to the third decimal place

checked according to the instructions for use specified in the relevant manual.

6 - PROCEDURE

6 - 1 Determination of the free iodine quantity

Into the titration beaker, exactly pipette 10 ml of potassium iodide and potassium chloride solution (4-2). Add about 25 ml distilled water (4-1) and perform the titration with the dilute iodine solution (4-4). When the titration is finished, note the potential values in accordance with the volume of iodine poured.

6 - 2 Determination of the free and the fixed iodine quantity

Into a 200-ml beaker, introduce an accurately weighed test portion ranging from 100 to 500 mg of defatted (*) starch depending on the assumed amylose content. Exactly add 50 ml of the potassium hydroxide solution (4-6) and stir for 2 hours with a magnetic stirrer. Then neutralise with exactly 100 ml of the hydrochloric acid solution (4-7) and stir for 1 to 2 minutes.

Into the titration beaker (5-3), exactly pipette 15 ml of this solution, add 10 ml of the 0.5 N potassium iodide solution (4-5) and about 10 ml of distilled water (4-1).

Perform the titration using the dilute iodine solution (4-4). Note the potential values and the volume of the dilute iodine solution poured to the equivalence potential.

7 - EXPRESSION OF RESULTS

7 - 1 Determination of the fixed iodine quantity

The fixed iodine quantity, expressed in mg, is given by the formula :

$$A = (V - V_0) \times \frac{T}{5}$$

where :

V = volume of iodine, in ml, poured in (6-2) to the equivalence potential

V_0 = volume of iodine, in ml, poured in (6-1) to the equivalence potential obtained in (6-2)

T = titre, in mg/ml, of the iodine solution (4-3)

5 = dilution ratio of the dilute iodine solution (4-4)

7 - 2 Amylose content

The amylose content, expressed as a percentage by mass of the dry product, is given by the formula :

$$\frac{A \times 150 \times 100 \times 100 \times 100}{1000 \times 19 \times P \times 15 \times DS}$$

where :

A = mass of iodine obtained in (7-1) (mg)
P = mass of the test portion (g)
19 = affinity of pure amylose to iodine
DS = dry substance of the test portion performed according to MCL 002B

8 - COMMENTS

* Defattening

Into a 250-ml flask with ground glass stopper, introduce 5 g starch, add 40 ml methanol at 85° GL (4-8). Heat under reflux for 4 h on a water bath at 70°C. Centrifuge, take up the deposit with 40 ml methanol at 85° GL and introduce into the 250-ml flask. Replace on the water bath, under reflux, at 70°C for 2 h, centrifuge, wash the deposit.

Once with 40 ml methanol at 85° GL (4-8),
3 times with 20 ml methanol at 85° GL (4-8),
7 to 8 times with 25 ml distilled water.

Place the deposit into a crystallizer, dry at 60°C, grind in a mortar and complete drying on the ground product.

9 – SAFETY – ENVIRONMENTAL PROTECTION

9 – 1 Safety

The use of equipments and chemical products mentioned in this method must be the subject of usual precautions (gloves, glasses, etc.).
All the information relating to these products is specified in the safety data sheets which are at the operators' disposal.

9 – 2 Environment

Some chemical products are collected in vessels provided for. This precaution is not applicable in this method.

9 - MODIFICATIONS

Modification references of the reagents in the chapter 4
Addition of chapter 9 - SAFETY – ENVIRONMENTAL PROTECTION

ROQUETTE

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LIST OF SIGNATURES

DATE	NAME(S)	SIGNATURE(S)	DATE	NAME(S)	SIGNATURE(S)